# Aza[6]helicene Platinum Complexes: Chirality Control of cis-trans Isomerism

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# Aza[6]helicene platinum complexes: chirality control of *cis-trans* isomerism**

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*Dedication((optional))*

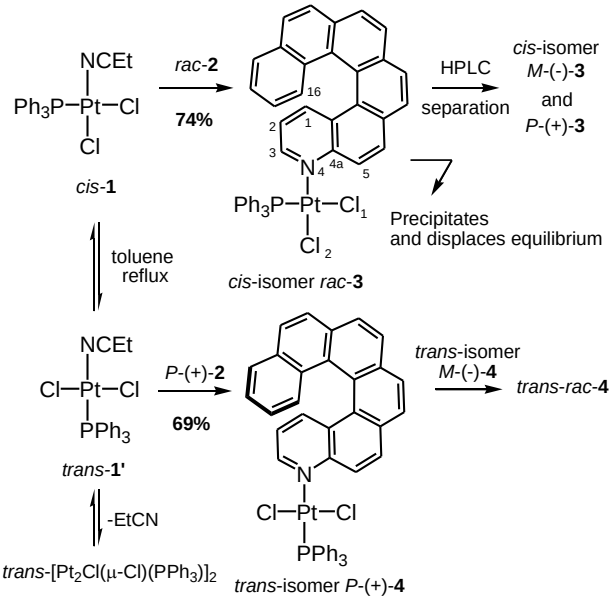
***Abstract**: It was serendipitously observed that cis-$PtCl_2$(NCEt)$PPh_3$ reacted differently with either racemic or enantiopure 4-aza[6]helicene giving respectively cis (racemic) and trans (enantiopure) 4-aza[6]helicene-bis-chloro-triphenylphosphine-platinum(II) complexes. This unexpected reactivity is explained through a dynamic process (crystallization induced diastereoselective transformation) and enables to address a new aspect of reactivity in chiral transition metal complexes.*

Square planar (SP-4) Pt(II) complexes of general formula LL'$PtX_2$ display the usual *cis*/*trans* isomerism that is well-known in coordination chemistry.[1] Such isomerism can have important practical implications such as in the famous case of $Pt(NH_3)_2Cl_2$ whose *cis* isomer is an efficient antitumor drug, while the *trans* isomer is ineffective.[2a,b] Therefore the control of the stereochemistry of SP-4 platinum complexes appears to be a pivotal step for the development of efficient drugs as well as innovative molecular materials.[2c,d]

Pure enantiomers and their racemic mixture are known to display different physical properties such as melting points and solubilities.[3] One can take benefit from these different physical properties to optimize, for instance, resolution processes of chiral molecules[3] or to perform uncommon reactivity such as amplification processes.[4a-d] In the liquid phase, identical physical and chemical properties are generally observed for pure enantiomers and their racemic mixture, except in those cases where strong homochiral and heterochiral associations take place.[4e] In addition, racemates and pure enantiomers may have different reactivity in solution such as, for example, in the asymmetric catalysis where non-linear effects may occur.[5]

In this communication, we show that the stereochemistry of the complexation of 4-aza[6]helicene ligand (**2**) with $PtCl_2$(NCEt)$PPh_3$ **1** depends dramatically on the state of **2**: indeed, racemic **2** leads to *cis*-$PtCl_2$(**2**)$PPh_3$ (*cis*-**3**), whilst enantiopure **2** leads to *trans*-$PtCl_2$(**2**)$PPh_3$ (*trans*-**4**). In other words, the *cis*/*trans* isomerism is here controlled by the enantiopure or racemic form of the azahelicene ligand. This is, at the best of our knowledge, a brand new aspect of chirality in transition metal complexes.

Helicene derivatives have recently shown potential interest as molecular materials due to their inherent chirality, large magnitude chiroptical properties and π-conjugated electronic structure.[6] Following our work aimed at understanding the impact on the chiroptical properties of a metallic ion upon coordination to a helicene ligand,[7a-b,f] we studied the complexation of 4-aza[6]helicene **2**[7c] as a monodentate N-ligand[7d,e] to a platinum(II) center.




**Scheme 1.** Synthesis of *cis*-isomer **3** and *trans*-isomer **4** in either racemic or enantiopure forms.

For this purpose, *cis*-$PtCl_2$(NCEt)$PPh_3$ complex (*cis*-**1**), a square planar platinum complex bearing a triphenylphosphine ligand and a propionitrile in mutual *cis* position, was used.[8] In refluxing toluene, it isomerizes to the *trans*-$PtCl_2$(NCEt)$PPh_3$ (*trans*-**1'**, Scheme 1**)**, which in turn may give the dimeric form *trans*-[PtCl($\mu$-Cl)($PPh_3$)]$_2$ after releasing EtCN. It is known that by reacting **1** with a pyridine ligand, the *trans*-$PtCl_2$(py)$PPh_3$ complex is formed and it does not isomerize to the *cis* form, probably due to the *trans*-effect of $PPh_3$ ligand.[8b] By replacing pyridine with azahelicene as the N donating ligand, an additional stereogenic element is introduced (*P*/*M* helical chirality) to the *cis*/*trans* isomerism and diastereoisomers *P-cis* and *P-trans* (and their corresponding mirror-images *M-cis* and *M-trans*) are expected. 4-Aza[6]helicene **2** was prepared in racemic form according to the well-known photocylization process (see SI).[7c] The reaction of $PtCl_2$(NCEt)$PPh_3$ **1** with a slight excess (1.2 eq.) of (±)-**2** in refluxing toluene for one night resulted in the precipitation of a

[*] D. Mendola, Dr. N. Saleh, Dr. Loïc Toupet, and Dr. J. Crassous
Sciences Chimiques de Rennes UMR 6226 - Institut de Physique de Rennes UMR 6251CNRS-Université de Rennes 1 Campus de Beaulieu 35042 Rennes Cedex, France
Fax: (+33) 223236939
E-mail: jeanne.crassous@univ-rennes1.fr
D. Mendola, Dr. F. Castiglione, Prof. A.Mele
Department of Chemistry, Materials and ChemicalEngineering «G. Natta», Politecnico di Milano, Piazza L. da Vinci, 32, I-20133 Milano, and CNR-ICRM Via L. Mancinelli, 7, I-20131 Milano, Italy
Prof. T. Caronna, Dipartimento di Ingegneria Industriale, Università di Bergamo, viale Marconi 5, 24044 Dalmine BG, Italy
Dr. N. Vanthuyne, Prof. C. Roussel
Chirosciences, UMR 7313, Stéréochimie Dynamique et Chiralité, Aix-Marseille University, 13397 Marseille Cedex 20, France

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yellow solid with 74% yield. This precipitate was identified as *cis*-isomeric complex **3** (Scheme 1) by multinuclear NMR spectroscopy, ESI-MS and X-ray crystallography. For instance, in the $^{1}$H NMR spectrum, a strongly deshielded doublet appears at 9.56 ppm ($^{3}J_{H\text{-}H}$ = 9.4 Hz) corresponding to H5 proton and a doublet of doublet at 8.45 ppm ($^{3}J_{H\text{-}H}$ = 5.4, $^{4}J_{H\text{-}H}$ = 1.4 Hz) corresponding to H3 (see numbering in Scheme 1). Furthermore, the $^{31}$P NMR displays one signal at 6.2 ppm with a $^{195}$Pt-$^{31}$P coupling constant of 3860 Hz. Single crystals were grown by slow evaporation of diisopropylether in a $CH_2Cl_2$ solution of **3.** The latter crystallized in the triclinic *P*-1 centro-symmetric space group with the presence of *M* and *P* azahelicenes. Its X-ray crystallographic structure depicted in Figure 1 reveals the square planar geometry around the platinum atom which is coordinated to two chlorine ligands being in a *cis* mutual position, one 4-aza[6]helicene ligand and one $PPh_3$. A little distortion from ideal angles of 90° is observed (N4PtP and N4PtCl1 angles of 94.8° and 85.2° respectively) presumably due to steric hindrance of ligands. Furthermore, *trans-influence* causes a greater bond length between platinum and the chlorine atom *trans* to phosphine (Pt-Cl1: 2.357 Å) than the corresponding one with the chlorine *trans* to the nitrogen atom (Pt-Cl2: 2.291 Å). These values are in agreement with similar complexes.[8d,e] Interestingly, weak intramolecular π–π interactions take place between one phenyl of the $PPh_3$ ligand and the pyridyl ring (centroid-centroid distance 3.852 Å). This interaction is only possible in the *cis* geometry complex and fixes the geometry around the platinum. Furthermore, due to the steric hindrance of the helix, the $PPh_3$ is stacked on one side of the pyridyl ring and therefore planar chirality appears with the pyPtCl2 defining the chiral plane.[9] Indeed, torsion angles of -86.16 and -80.93° (p*M*-chirality) are measured respectively for C3NPtP and C4aNPtCl1 in the *cis*-**3** molecule having the *M*-4-aza[6]helicene ligand, which means that the *M*-helicity induces a fixed p*M*-chiral planar sense.[10] All four possible stereoisomers (two diastereomeric pairs of enantiomers) are depicted in Figure 1c. This efficient chiral induction from the helix to the planar chirality around the Pt center is also reflected in the chiroptical properties (*vide infra*). Finally, looking more into details the crystal packing of **3** reveals a set of several different intermolecular CH...Cl hydrogen bonds that contribute to the cohesion and the stability of the crystal (Figure 2d). In solution, NOESY experiments performed in $CD_2Cl_2$ allow to evidence contacts *i*) between H1 and H16 atoms belonging to opposite sides of the aza[6]helicene moiety and *ii*) between Ha protons of the $PPh_3$ ligand and protons H3 and H5 of the aza[6]helicene (Figure 2a). This indicates that the preferred conformation of racemic *cis*-**3** in the solid state is also stable in solution. Overall, these interactions are responsible for the fixed *cis* geometry, stability and low solubility in toluene of the racemic complex **3**. Finally, ESI mass spectrometry afforded a peak at *m/z* 880.0 corresponding to sodium cationized $[PtCl_2(\mathbf{2})P(Ph)Na]^+$ of elemental composition corresponding to $[C_{43}H_{30}NPCl_2PtNa]^+$ and with an excellent match between the calculated and the experimental isotopic cluster (see SI). Tandem MS experiments were carried out on the monoisotopic ion at *m/z* 880.0 isolated in the ion trap and allowed to decompose via collision with He gas. In these conditions, the peak at *m/z* 330 was detected, corresponding to protonated **2**, thus confirming the presence of the aza[6]helicene ligand in the complex.

With the aim to prepare enantiomerically pure complexes, the *M*-(-) and *P*-(+)-**2** enantiomers were separated by HPLC over a chiral stationary phase (see SI). Then the reaction between **1** and *P*-(+)-**2** was performed in the same conditions as reported for the racemic ligand (see SI). To our surprise, no yellow precipitate was observed and a new compound **4** was isolated in 69 % yield after purification, which displayed different $^{1}$H, $^{13}$C and $^{31}$P NMR spectra from *cis*-**3** (see SI)

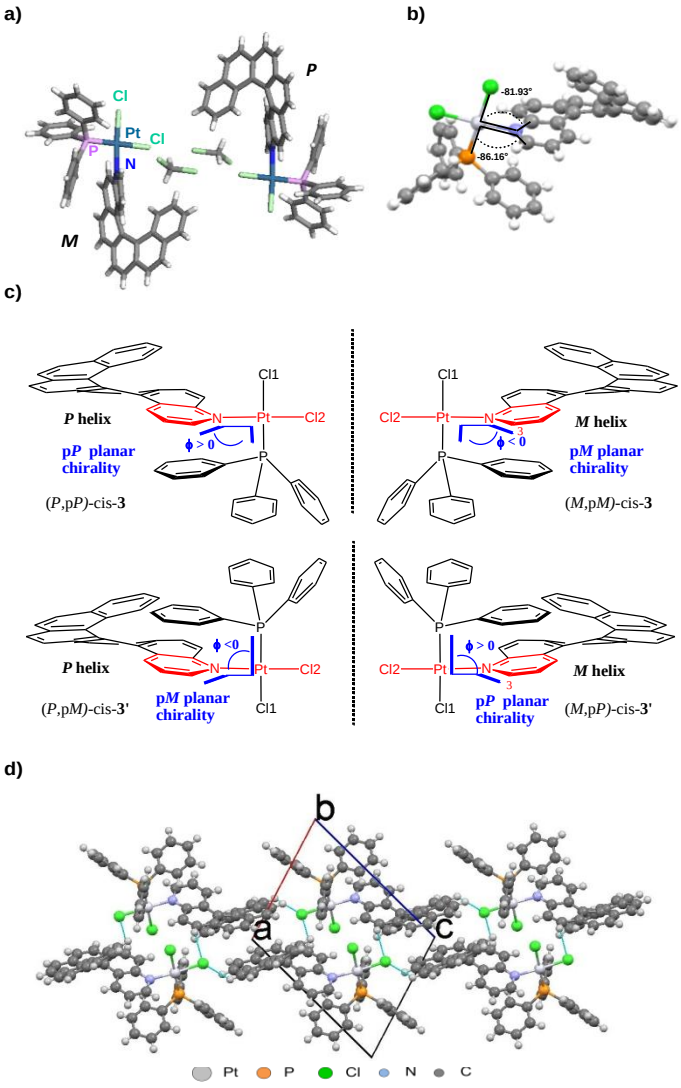


**Figure 1.** a) X-ray crystallographic structure of racemic *cis*-$PtCl_2$(**2**)($PPh_3$) **3** with the *P* and *M* helicene complexes in the unit cell. b) p*M* planar chirality around the Pt center.[10] c) Drawings emphasizing the helical and planar chiralities and all four possible stereoisomers. The (*P*,p*M*)- and (*M*,p*P*)-*cis*-**3'** stereoisomers are not observed. d) Selected view of the crystal packing and CH...Cl hydrogen bonds.

The $^{1}$H NMR spectrum displayed one doublet at 9.60 ppm for H5 ($^{3}J_{H\text{-}H}$ = 9.1 Hz) and one signal (ddd) at 8.90 ppm ($^{3}J_{H\text{-}H}$ = 5.4, $^{4}J_{H\text{-}H}$ = 1.5 Hz; $^{4}J_{H\text{-}P}$ = 3.8 Hz) for H3. $^{31}$P NMR displays one signal at 2.6 ppm with a $^{195}$Pt-$^{31}$P coupling constant of 3640 Hz, significantly different to that observed for *cis*-**3**. ESI mass spectrometry gave once again a peak at *m/z* 880.0 with isotopic cluster consistent with $[C_{43}H_{30}NPCl_2PtNa]^+$. Isolation and collision induced fragmentation of monoisotopic *m/z* 880 gave the same fragmentation pattern as before, thus giving arguments in favor of their isomeric relationship and suggesting that the new compound corresponds to the *trans* isomer *P*-(+)-**4** (Scheme 1). Although no crystal structure was obtained for this compound, either enantiopure or racemic, several further information ascertain the *trans* geometry. Long-range NOEs were selectively observed in $CD_2Cl_2$ solution between Ha($PPh_3$) and H5, but not between Ha($PPh_3$) and H3, consistent with the *trans* geometry shown in Figure 2b. The assignment of the stereochemistry on the basis of NOEs was supported by DFT calculations on both **3** and **4** (see SI). According

to the intramolecular NOE theory,[11] the NOE intensity of two H nuclei separated by a distance $r$ shows $r^{-6}$ dependency. As a consequence, the threshold of about 5Å for vanishing NOE is commonly accepted. For the sake of clarity, the average calculated distance of H3 with the Ha protons of the phenyl groups of triphenylphosphine were below and above 5Å for isomer *cis*-**3** and *trans*-**4**, respectively. Furthermore, coupling constants $^4J_{H\text{-}P}$ (3.8 Hz) and $^5J_{H\text{-}P}$ (1.4 Hz) are observed in complex **4** for H3 and H2 protons respectively in the $^1$H NMR spectrum (confirmed by $^{31}$P decoupling experiments), not observable in the *cis*-**3** isomer. $^4J_{H\text{-}P}$ have been reported for complex *trans*-$PtCl_2(SO(CH_3)_2)(PCy_3)$, (Cy = cyclohexyl)[8b] and this further corroborates the hypothesis of a *trans*-geometry for complex *P*-(+)-**4**. Finally, the *trans* nature of **4** was unambigously confirmed thanks to a sample prepared by reacting (±)-**2** with pure *trans*-$[Pt(PPh_3)(\mu\text{-}Cl)Cl]_2$[8c] which displayed the same $^1$H and $^{31}$P NMR spectra as *P*-(+)-**4**. This compound can only be the racemic *trans*-complex due to the strong *trans* effect of $PPh_3$ (equation 1).

$$trans\text{-}[Pt_2Cl(\mu\text{-}Cl)(PPh_3)]_2 \xrightarrow[CD_2Cl_2]{rac\text{-}\mathbf{2}\ (2\ eq.)} trans\text{-isomer } rac\text{-}\mathbf{4} \qquad (1)$$

It is worth of mention that it was impossible to observe any *P*- or *M*-*cis*-isomer **3** from the reaction mixture with enantiomerically pure ligand **2**, even by performing the reaction at -50° C. Furthermore, heating pure samples of **3** or **4** did not result in any changes, suggesting that **3** and **4** are not in equilibrium. However, deeper inspection of the crude mixture from the reaction of *rac*-**2** with **1** revealed the presence of small quantities (<5%) of the racemic *trans*-**4** ($^1$H- and $^{31}$P NMR spectra in SI). As a consequence, the formation of large quantities of *trans*-**4** is prevented by the spontaneous precipitation of *cis*-**3** in refluxing toluene which displaces the **1**/**1'** equilibrium (see Scheme 1). This process corresponds to a crystallization induced diastereoselective transformation[12] and originates from the *cis*/*trans* lability of the starting material.

Finally, the mirror-imaged *trans*-*M*-(-)-**4** complex was obtained starting from *M*-(-)-**2**. On the other hand, the enantiopure *P*-(+) and *M*-(-) *cis* complexes **3** were separated by HPLC over a chiral stationary phase (see SI). This nicely illustrates how the chirality of the ligand (racemic *vs.* enantiopure) can be used to obtain the all set of *cis* and *trans* isomeric Pt complexes in either racemic or enantiopure forms.

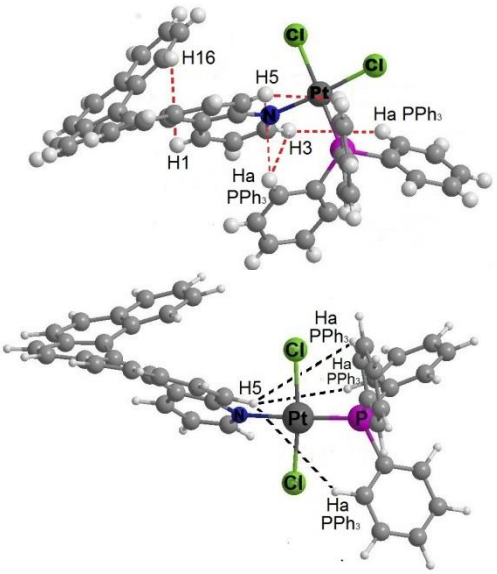


**Figure 2.** Selected, long-range NOEs (dashed lines) detected in a) *cis*-$PtCl_2$(**2**)($PPh_3$) **3** and b) in *trans*-$PtCl_2$(**2**)($PPh_3$) **4**. The structures of both isomers are based on DFT calculations (the crystal structure coordinates were taken as starting geometry for **3** only).

The chiroptical properties (electronic circular dichroism ECD and molar rotations MR) of *P*-(+)/*M*-(-) enantiomers of ligand **2** and *cis* and *trans* isomeric complexes **3** and **4** were then examined (Figure 3). Ligand *P*-**2** displays a strong negative CD-active at 258 nm ($\Delta\varepsilon$ = -110 $M^{-1}cm^{-1}$) and strong positive bands at 310, 325 and 348 nm (+46, +150, +66 $M^{-1}cm^{-1}$). Complex *P*-**3** displays the same strong negative band of similar intensity (260 nm, $\Delta\varepsilon$ = -120 $M^{-1}cm^{-1}$) and strong positive bands at 319, 337, 351 nm that are red-shifted and of lower intensities (50, 78, 82 $M^{-1}cm^{-1}$) compared to *P*-**2**. The CD spectrum of complex *P*-**4** shows the same overall shape as *P*-**3** but with lower intensity ($\Delta\varepsilon$ = -57 $M^{-1}cm^{-1}$ at 258 nm, and 32, 54, 50 $M^{-1}cm^{-1}$ at 317, 336, 348 nm respectively). Two additional weakly CD-active bands at 398 and 420 nm are present in the three compounds. Similarly, lower molar rotation values were measured for *P*-**4** as compared to *P*-**3** (5870 *vs.* 8215 (±5%), $CH_2Cl_2$, *C* 0.7-0.4) while ligand *P*-**2** displays values comparable to similar aza[6]helicene derivatives (7735 (±5%), $CH_2Cl_2$, *C* 1.7).[7b] The bigger chiroptical properties of *cis*-**3** compared to *trans*-**4** may be explained by the fixed planar chirality present in *cis*-**3** that furnishes additional contributions to the ECD and MR values.

In conclusion, the enantiopurity of the starting helicenic ligand (racemic *vs.* enantiopure) triggers its reactivity *vs. cis*/*trans* isomers formation, thus allowing us to prepare the all set of four *P*-(+)/*M*-(-)-*cis* and *P*-(+)/*M*-(-)-*trans* isomeric (4-aza[6]helicene)-*bis*-chloro-triphenylphosphine-platinum(II) complexes and finally to examine their chiroptical properties in relation with their helical/planar chirality. To our knowledge, this is an unprecedented use of chirality in transition metal complexes, which combines the different solubilities between *cis*/*trans* stereoisomers with the configurational lability of the starting materials. We think that this can be often encountered in transition metal complexes and should be more accurately examined when geometrical isomerism (*cis*/*trans*, *fac*/*mer*)[9,10] is combined with chirality (*R*/*S*, *Δ*/*Λ*, *M*/*P*).

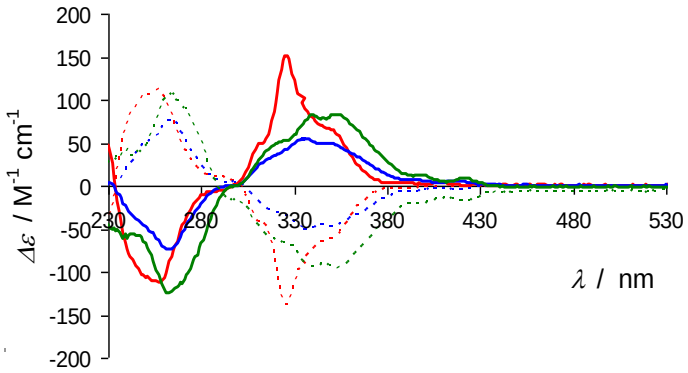


**Figure 3.** CD spectra of *P*-(+) (plain lines) and *M*-(-) (dotted lines) of ligand **2** (red), *cis* isomer complex **3** (green) and *trans* isomer complex **4** (blue).

**Keywords:**Helicenes•Chirality•Complexation•*Cis*/*trans* isomerism•Platinum


[1] (a) R. H. Crabtree, The organometallic chemistry of the transition metals, Wiley Interscience, **2005** (4th edition). (b) M. Melnik, C. E. Holloway, *Coord. Chem. Rev.* **2006**, *250*, 2261. (c) J. J. Wilson, S. J. Lippard, *Chem. Rev.* **2014**, *ASAP*, DOI**:** 10.1021/cr4004314.

[2] (a) B. Lippert, *Coord. Chem. Rev.* **1999**, *182*, 263. (b) Z. Guo, P. J. Sadler, *Angew. Chem. Int. Ed.* **1999**, *38*, 1512. (c) C. L. Ho, W. Y. Wong, *Coord. Chem. Rev.* **2013**, *257*, 1614. (d) T. C. Johnstone, S. J. Lippard, *J. Am. Chem. Soc.* **2014**, *136*, 2126.

[3] These differences are well-represented by their phase diagram which defines if a chiral molecule is either a conglomerate, a racemic mixture or a solid solution. See: J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates, & Resolutions*, J. Wiley & Sons, New York, **1981**.

[4] (a) P. Cintas, C. Viedma, *Chirality* **2012**, *24*, 894 and references therein. (b) M. Avalos, R. Babiano, P. Cintas , J. L. Jimenez, J. C. Palacios, *Tetrahedron: Asymmetry* **2010**, ***21***, 1030 and references therein. (c) B. L. Feringa,R. A. van Delden, *Angew. Chem. Int. Ed.* **1999**, *38*, 3419. (d) F. Caprioli, A. V. R. Madduri, A. J. Minnaard, S. R. Harutyunyan, *Chem. Commun.* **2013**, *49*, 5450. (e) V. Soloshonok, C. Roussel, O. Kitagawa, A. Sorochinsky, *Chem. Soc. Rev.* **2012**, *41*, 4180.

[5] (a) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2923. (b) D. Guillaneux, S. H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430. (c) D. G. Blackmond *Tetrahedron: Asymmetry* **2010**, *21*, 1630 and references therein.

[6] Selected reviews: (a) Y. Shen, C. -F. Chen, *Chem. Rev.* **2012**, *112*, 1463. (b) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 1051. (c) I. G. Stará, I. Starý, in: J. S. Siegel, Y. Tobe (Eds.), *Science of Synthesis*, vol. 45, Thieme, Stuttgart, **2010**, pp. 885-953. (d) A. Rajca, M. Miyasaka, in: T. J. J. Müller, U. H. F. Bunz (Eds.), *Functional Organic Materials* Wiley-VCH, Weinheim, **2007**, pp. 543-577. (e) A. Urbano, *Angew. Chem. Int. Ed.* **2003**, *42*, 3986. (f) T. J. Katz, *Angew. Chem. Int. Ed.* **2000**, *39*, 1921. (g) R. H. Martin, *Angew. Chem. Int. Ed.* **1974**, *13*, 649.

[7] (a) S. Graule, M. Rudolph, N. Vanthuyne, J. Autschbach, C. Roussel, J. Crassous, R. Réau, *J. Am. Chem. Soc.* **2009**, *131*, 3183. (b) S. Graule, M. Rudolph, W. Shen, C. Lescop, J. A. G. Williams, J. Autschbach, J. Crassous, R. Réau, *Chem. Eur. J.* **2010**, *16*, 5976. (c) R. H. Martin, M. Deblecker, *Tetrahedron Lett.* **1969**, *41*, 3597. (d) J. Misek, F. Teply, I. G. Stara, M. Tichy, D. Saman, I. Cisarova, P. Vojtisek, I. Stary, *Angew. Chem. Int. Ed.* **2008**, *47*, 3188. (e) T. Caronna, F. Castiglione, A. Famulari, F. Fontana, L. Malpezzi, A. Mele, D. Mendola, I. Natali Sora, *Molecules* **2012**, *17*, 463. (f) V. Vreshch, M. El Sayed Moussa, B. Nohra, M. Srebro, N. Vanthuyne, C. Roussel, J. Autschbach, J. Crassous, C. Lescop, R. Réau, *Angew. Chem. Int. Ed.* **2013**, *52*, 1968.

[8] (a) V. K. Jain, L. Jain, *Coord. Chem. Rev.* **2005**, *249*, 3075. (b) J. A. Davies, A. Sood, *Inorg. Chem.* **1985**, *24*, 4213. (c) D. Belli Dell'Amico, L. Labella, F. Marchetti, S. Samaritani, *Dalton Trans.* **2012**, *41*, 1389. (d) Dell'Amico, C. Broglia, L. labella, F. Marchetti, D. Mendola, *Inorg. Chim. Acta* **2013**, *395*, 181. (e) U. Belluco, R. Bertani, F. Meneghetti, R. A. Michelin, M. Mozzon, G. Bandoli, A. Dolmella, *Inorg. Chim. Acta* **2000**, *300-302*, 912.

[9] For axial and planar chirality in SP-4 complexes see: (a) M. C. Biagini, M. Ferrari, M. Lanfranchi, L. Marchio, M. A. Pellinghelli, *J. Chem. Soc., Dalton Trans.* **1999**, 1575. (b) E. C. Constable, *Chem. Soc. Rev.*, **2013**, *42*, 1637.

[10] (a) A. von Zelewsky, *Stereochemistry of Coordination Compounds*, J. Wiley&Sons, Chichester, **1996**. (b) A. Amouri, M. Gruselle, *Chirality in Transition Metal Chemistry: Molecules, Supramolecular Assemblies and Materials*, Wiley-VCH, **2009**. (c) V. I. Sokolov, *Chirality and Optical Activity in Organometallic Compounds*, Gordon and Breach Science Publishers, **1990**. (d) The p label in p*M* and p*P* is used to differentiate planar from helical chirality.

[11] D. Neuhaus and M. P. Williamson *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, 2nd edition, Wiley-VCH, **2000**.

[12] K. M. J. Brands, A. J. Davies, *Chem. Rev.* **2006**, *106*, 2711